GASTRIC ESOPHAGEAL REFLUX DISEASE:

DEFINITION:

- Condition that develops when the reflux of gastric content causes troublesome symptoms or complications
- Heartburn & regurgitation are principal symptoms of GERD
  - Heartburn = burning sensation in chest or upper abdomen
  - Regurgitation = perception of gastric contents in mouth or hypopharynx
- Acid reflux is most common cause of heartburn

TYPES OF REFLUX DISEASE:

1) Esophageal injury (30%):
   a. Reflux esophagitis
   b. Reflux strictures
   c. Barrett's esophagitis
   d. Esophageal adenocarcinoma
2) Absence of esophageal lesions (70%)
   a. Nonerosive reflux disease (NERD)

REFLUX DISEASE AND PAIN:

- Only about 50% of acid reflux episodes seem to evoke pain
  - Low pH activates chemoreceptors to evoke pain
  - Severity of pain increases as pH lowers
    - pH of 6 can evoke pain in 40% of patients
- Loss of mucosal barrier activates nociceptors (TRPV1 receptor) → esophageal distension and sustained esophageal contractions → heartburn pain through activation of mechanoreceptors
  - Stress increases perception of heartburn and may act to alter esophageal mucosal barriers
- Chronic exposure to low pH, bilirubin, proteases & mechanical stimuli sensitize the esophagus, lowering pain thresholds
- ACh and pain:

Edrophonium	Atropine
Short-acting cholinesterase inhibitor that increases cholinergic mediated esophageal (and GI) smooth muscle contractions and increases gastric acid secretion	Muscarinic receptor antagonist that inhibits cholinergic mediated esophageal contractions and also decreases gastric acid secretion
= Increased pain sensitivity	*= Decreased pain sensitivity*

TREATMENT OF ESOPHAGITIS:

- Esophageal healing can be achieved with acid neutralization
  - Antacids, H2 antagonists, PPIs
    - PPIs are most effective agents for treatment (symptomatic relief in 70-80% of patients)
  - Symptoms recur after discontinuation of all treatment
  - Intermittent courses for recurrent symptoms required
- Prokinetic agents (speed gastric emptying) used mainly in combination with PPIs or H2 blockers in patients with regurgitation or refractory heartburn

► Symptom severity (pain, heartburn) correlates poorly with presence and severity of esophagitis

► Symptoms can persist despite healing of lesions

PEPTIC ULCER DISEASE:

TYPES OF ULCERS:

- Duodenal ulcers are 4 times more common than gastric ulcers
- Duodenal ulcers occur in young adults, gastric ulcers in older adults
- Both types of ulcers are more common in men

SYMPTOMS:

- Epigastric pain relieved by food intake or antacids
- Pain between meals and/or that causes awakening at night
- Loss of appetite and weight loss

MORE SEVERE ULCERATION:

- Anemia, hematemesis, melena, hemepositive stool = maybe bleeding
- Severe radiating pain = maybe perforation (→ peritonitis)

MUCUS-BICARBONATE-PHOSPHOLIPID "BARRIER":

- Prostaglandins (PGE2, PGI2) enhance gastric mucosal protection by:
  - Stimulating mucus production
  - Bicarbonate secretion (EP1 receptor)
  - Epithelial cell proliferation
  - Increasing mucosal blood flow

CAUSES:

Mucosal damage	• Stomach & proximal duodenum most common

H. pylori infection (50%)	• H pylori found in stomach of 50% of population
	• Infection leads to gastritis which disrupts acid homeostasis
	  ○ Increases gastrin levels (more H+ production)
	  ○ Decreases gastric mucus production
	  ○ Decreases duodenal mucus bicarbonate secretion = favors ulcer formation
	• Eradication of infection reduces ulcer recurrence

NSAIDs (5-20% on long-term therapy)	• Inhibits cyclooxygenase, decreasing levels of prostaglandins (= decreased gastric mucosal production) • Can co-exist with H pylori infection = increase risk of ulceration
Stress	• Critical illness, surgery or hypovolemia → splanchnic hypoperfusion → stress ulcers
Smoking	• Exacerbates and slows healing

TREATMENT OF PEPTIC ULCER DISEASE:

Ulcers	PPIs heal > 90% duodenal (4 wk) and gastric (6-8 wks) ulcers
H.pylori	10-14 day regimen of "triple therapy" (PPI, clarithromycin and amoxicillin or metronidazole), then PPI x 4-6 weeks
NSAID	• Discontinue NSAID • PPIs reduce incidence of ulcers & ulcer complications in pts taking aspirin or other NSAIDs
Stress	• PPIs and H2 antagonists (similar efficacy) • Mucosal protective agents (sucralfate)

MECHANISM OF ACTION OF SPECIFIC DRUGS:

ANTACIDS:
- Non-prescription remedies for treatment of intermittent heartburn and dyspepsia
- Antacids = weak bases that react with gastric HCl to form a salt and water (which then neutralizes acid)

SODIUM BICARBONATE (baking soda):
- Reacts rapidly with HCl to produce CO_2
- Results in gastric distension and belching
- High doses may cause metabolic alkalosis

CALCIUM CARBONATE (Tums):
- Slow reaction with HCl to form CO_2 & $CaCl_2$
- May cause belching or metabolic alkalosis

MAGNESIUM HYDROXIDE ± ALUMINUM HYDROXIDE
- React slowly with HCl to form magnesium chloride or aluminum choride and water
- No gas is generated = no belching
- Metabolic alkalosis is also uncommon
- Combination preferred because:
  - Unabsorbed magnesium salts may cause osmotic diarrhea
  - Aluminum salts may cause constipation
- Al and Mg absorbed and excreted by kidneys = problem in renal failure
- Salts bind many drugs and iron

POTASSIUM-COMPETITIVE ACID BLOCKERS (P-CABs):
- Soraprazan, revaprazan, vonoprazan
- Compete with K+ for binding site on proton pump
- Fast onset of action, full effect with 1st dose
- May have greater acid suppression than PPIs

MUCOSAL PROTECTIVE AGENTS: sucralfate

MECHANISM OF ACTION:
1. Sucrose complexed to sulfated aluminum hydroxide → breaks down into sucrose sulfate (strongly negatively charged)
2. Binds to +ve proteins in base of ulcer and forms a physical barrier that restricts further damage

USES:
- Administered as slurry through nasogastric tube to reduce stress ulcers in pts at risk from infxn
- Avoids use of antacids, H2 antagonists or PPIs

ADVERSE EFFECTS: not absorbed = few systemic AEs
- Constipation occurs rarely

PROSTAGLANDIN ANALOGUES: misoprostil
- Prostaglandin derivative that is cytoprotective and inhibits gastric acid secretion
- EP (EP1 & EP3) receptors responsible for its actions
- Used for prevention of NSAID-induced peptic ulcers

ERYTHROMYCIN: prokinetic agent
- Directly stimulates motilin receptors on GI smooth muscle → accelerates gastric emptying

USES:
- Gastroparesis (slowed stomach emptying) but tolerance rapidly develops
- Acute upper GI hemorrhage to promote gastric emptying of blood prior to endoscopy

PROTON PUMP INHIBITORS (PPI): omeprazole

MECHANISM OF ACTION:
1. Inactive acid-labile pro-drug (lipophilic weak base)
2. EC for delayed release in intestinal lumen
3. After intestinal absorption, diffuses readily across lipid membrane into acidified compartments
   (ex// parietal cell canaliculus)
4. Protonated, concentrated and converted to reactive thiophilic sulfonamide cation
5. Sulfonamide forms covalent disulfide linkage with H^+K^+ATPase pumps
   - Recovery = new proton pump synthesis
   - Only proton pumps actively secreting acid are susceptible to inhibition

ONSET OF ACTION:
- Drug dose not affect other (non-GI) proton pumps
- Maximal activity of proton pump occurs during meal, so give 1 hour before a meal
- Duration of acid inhibition lasts up to 24 h
  - ~ 18h to synthesize new pump molecules
- Not all proton pumps inactivated with the first dose (3-4 days for maximal inhibition)

ADVERSE EFFECTS OF PPIs:
- Diarrhea, headache, abd. pain (similar to placebo)
- Subnormal B12 levels due to decreased absorption (*clinical relevance??)*
- Infections due to loss of gastric acid barrier to bacterial colonization (*clinical relevance?)*

H2 RECEPTOR ANTAGONISTS: ranitidine, famotidine

MECHANISM OF ACTION:
- Highly selective, competitive inhibitor at parietal cell H2 receptors (no effect on H1/H3)
  - NOTE: activation of H2 on parietal cells promotes gastric acid release
- Reduced histamine released from ECL cells
  - Block direct stimulation of parietal cell by histamine
- Suppresses basal (90%) and meal-stimulated (80%) acid secretion in a linear, dose-dependent manner = overall each dose suppresses acid release by 50% for ~ 10 h

CURRENT USES:
- Peptic and duodenal ulcers: 2nd line after PPIs
- Gastro-esophageal reflux disease
- Dyspepsia (indigestion): OTC treatment but not clear if better than placebo
- Stress-related ulcers: develop in seriously ill patients in ICU
  - Significantly reduce incidence of bleeding from stress-related gastritis

ADVERSE EFFECTS OF H2 ANTAGONISTS:
- 3% get diarrhea, headache, fatigue, myalgias or constipation
- Confusion, hallucinations, agitation may occur in ICU or elderly patients
- Bradycardia occurs as a result of blocking H2 receptors, but rarely clinically important
  - Can occur with rapid IV infusion
- Agents cross placenta and accumulate in breast milk

PROKINETIC AGENTS: drugs that stimulate gut motor function and/or improve gastric emptying
► Muscarinic agonists, dopamine D2 antagonists, 5-HT4 receptor agonists (Cisapride)

DOPAMINE D2 RECEPTOR ANTAGONISTS: metoclopramide & domperidone
- DA receptors inhibit cholinergic smooth muscle stimulation
  - Blockade of D2 receptors enhances effect of ACh release to increase: esophageal peristaltic amplitude & sphincter, pressure & gastric emptying (= can also be used for impaired gastric emptying)
  - No effect upon small intestine or colonic motility
- Metoclopramide may also block D2 receptors in CRTZ (antinausea & antiemetic)

ADVERSE EFFECTS:
- Metoclopramide: CNS (restlessness, drowsiness, insomnia, anxiety, agitation, EPS)
- Domperidone: well-tolerated (does not cross the BB)
- Both: elevate prolactin levels & may cause breast tenderness and enlargement, galactorrhea (uncommon) and menstrual irregularities (including amenorrhea)